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REVISED DIAGNOSTIC CRITERIA FOR THE MARFAN SYNDROME

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ABSTRACT

In 1986, the diagnosis of the Marfan syndrome was codified on the basis of clinical criteria in the Berlin nosology [Beighton et al., 1988]. Over time, weaknesses have emerged in these criteria, a problem accentuated by the advent of molecular testing. In this paper, we propose a revision of diagnostic criteria for Marfan syndrome and related conditions. Most notable are: more stringent requirements for diagnosis of the Marfan syndrome in relatives of an unequivocally affected individual; skeletal involvement as a major criterion if at least 4 of 8 typical skeletal manifestations are present; potential contribution of molecular analysis to the diagnosis of Marfan syndrome; and delineation of initial criteria for diagnosis of other heritable conditions with partially overlapping phenotypes.

KEY WORDS: Marfan syndrome, diagnosis, aortic aneurysm, mitral valve prolapse, ectopia lentis, dural ectasia, heritable disorders of connective tissue.

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INTRODUCTION

In 1896, the first professor of pediatrics in France, Antoine Marfan, presented the case of a 5-year-old girl to the Société Médicale des Hôpitaux de Paris [Marfan; 1896]. This child, Gabrielle P., had striking abnormalities of the skeletal system which progressed to the time of her death in early adolescence, probably from tuberculosis [Marfan, 1938]. Whether Gabrielle was affected by what became known as the Marfan syndrome has never been clarified. Indeed, she perhaps had congenital contractural arachnodactyly [Hecht and Beals, 1972]. During the 20th century, additional manifestations were recognized as frequent components of the phenotype of the Marfan syndrome--ectopia lentis [Börger, 1914], autosomal dominant inheritance [Weve, 1931], aortic dissection [Etter and Glover, 1943] and dilatation [Baer et al.,1943], mitral valve prolapse [Brown et al., 1975; Pyeritz and Wappel, 1983] and dural ectasia [Pyeritz et al., 1988]. Weve [1931] first suggested that the basic cause of Marfan syndrome lay in a defect in the mesoderm, and McKusick [1955] included the condition as a charter member of his new nosologic grouping, the heritable disorders of connective tissue. Until the past few years, the diagnosis of the Marfan syndrome has relied

completely on clinical criteria, codified in 1986 in the so-called Berlin Nosology [Beighton et al., 1988]. As useful as these criteria proved to be, several shortcomings remained and others have emerged. Any set of criteria based solely on individual opinion and collective discussion is likely flawed to some degree. The nature of this phenotype, a continuum that, at the mild end of the spectrum, merges with the normal population, is one problem. Another is the existence of a number of autosomal dominant connective tissue disorders defined primarily by one of the major manifestations of the Marfan syndrome, but lacking a broad range of systemic involvement [Pyeritz, 1996]. Establishing the lines separating normal variation from mild connective tissue phenotypes from Marfan syndrome is arbitrary to some degree. Moreover, the advent of molecular analysis has not been a panacea [Dietz and Pyeritz, 1995].

The discovery of the cause of the Marfan syndrome was greatly assisted by the Berlin Nosology; the first step involved linkage analysis, and having criteria for assigning affected status in large pedigrees was essential for localizing the gene causing Marfan syndrome to 15q21 [Kainulainen et al., 1990 ; Dietz et al., 1991a]. Similarly, when mutations in the gene encoding the microfibrillar protein fibrillin-1, which also mapped to 15q21, were first reported, uniform adherence to the existing diagnostic criteria gave considerable assurance that the *FBN1* gene was the cause of Marfan syndrome [Dietz et al., 1991b]. However, additional mutations have been discovered in *FBN1* and the gene for a related protein, fibrillin-2 (*FBN2*), in individuals who do not meet Berlin Nosology criteria for Marfan syndrome [Dietz and Pyeritz, 1995; Pyeritz, 1996]. Conditions already considered distinct from Marfan syndrome, such as congenital contractural arachnodactyly (CCA) and familial mitral valve prolapse syndrome (or MASS phenotype) can be due to mutations in these genes [Putnam et al., 1995]. Of most concern were the misdiagnoses of relatives that arose by relying solely on Berlin Nosology after unequivocal diagnosis of a first-degree relative [Pereira et al., 1994; Dietz et al., 1995]. Molecular evidence showed that the criterion of a positive family history could produce a bias in favor of overdiagnosis.

Since molecular [Dietz et al., 1993; Francke et al., 1995; Nijbroek et al., 1995] and therapeutic developments [Shores et al., 1994; Silverman et al., 1995] have further enhanced the need for reliable, uniform diagnostic criteria, we have tried to address the shortcomings of the Berlin Nosology. In this article, we propose revised criteria that are still based on a combination of major and minor clinical manifestations in different organ systems. The major differences in this new version are:

- more stringent requirements for diagnosis of the Marfan syndrome in relatives of an unequivocally affected individual;
- skeletal involvement as a major criterion if at least 4 of 8 typical skeletal manifestations are present;
- potential contribution of molecular analysis to the diagnosis of Marfan syndrome; and
- delineation of initial criteria for diagnosis of other heritable conditions with partially overlapping phenotypes.

METHODS

The authors produced a draft set of criteria arrived at through discussion and consensus. The preliminary guidelines were then circulated to other professionals working in the field and presented at scientific meetings. Criticisms were considered by the authors and incorporated when there was consensus to do so.

REVISED DIAGNOSTIC CRITERIA

These criteria, as in the previous version, are based largely on clinical findings in the various organ systems, and in the nature of the family history and relationships. A "major" criterion is one that carries high diagnostic specificity, because it is relatively infrequent in other conditions and in the general population. A nuance in this revision is the conversion of a number of minor criteria in the skeletal system into a major criterion.

There is an important distinction between a major criterion being present in a system, and the system "being involved". The latter, while important in the diagnostic decision matrix, is less important than having an evident major criterion.

Skeletal System

Major criterion. Presence of at least 4 of the following manifestations.

- pectus carinatum
- pectus excavatum requiring surgery
- reduced upper to lower segment ratio or arm span to height ratio greater than 1.05
- wrist and thumb signs
- scoliosis of > 20° or spondylolisthesis
- reduced extension at the elbows (< 170°)
- medial displacement of the medial malleolus causing pes planus
- protrusio acetabulae of any degree (ascertained on radiographs)

Minor criteria.
- pectus excavatum of moderate severity
- joint hypermobility
- highly arched palate with crowding of teeth
- facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-Slanting palpebral fissures)

For the skeletal system to be considered involved, at least 2 of the components comprising the major criterion or one component comprising the major criterion plus 2 of the minor criteria must be present.

Comments. Many skeletal anomalies are common in the population; thus, a combination of defects is necessary to achieve diagnostic specificity. Joint hypermobility is a good example of a common and generally benign sign that carries, by itself, little weight. Alternatively, congenital joint contractures are much less common in the population, but occur with moderate frequency in the Marfan syndrome. The elbow is most often affected by contracture; the importance of camptodacyly of the 4th and 5th digits is less certain. An important secondary point is that not all joint hypomobility in association with other skeletal anomalies means the subject has congenital contractural arachnodactyly (CCA). The anterior chest deformity is most characteristic when asymmetric, with the sternum tilted in the axial plane and the left costochondral junctions more anterior. Measurements of stature and span are taken from the 1988 anthropometric survey of US Army personnel [Gordon et al., 1990]. Upper segment/lower segment ratio for patients and unaffected people of all ages as provided by McKusick [1956; 1972] and reprinted widely [Hall et al., 1989; Pyeritz, 1993; 1996]. The wrist sign requires that the thumb overlaps the terminal phalanx of the fifth digit when grasping the contralateral wrist [Walker and Murdoch, 1970]. The thumb sign requires that the entire nail of the thumb projects beyond the ulnar border of the hand when the hand is clenched without assistance, a slight modification of the original description [Steinberg, 1966]. Scoliosis of some degree (generally thoracic, convex to the right) occurs in at least 60% of patients. Abnormal sagittal curvature, such as thoracic hypo- or hyperkyphosis is also common. Spondylolisthesis occurs in about 6% [Sponseller et al., 1995]. A plain radiograph (anteroposterior) of the pelvis is the simplest means of detecting protrusio acetabuli, and should be performed when finding this sign would aid in diagnosis [Kuhlman et al., 1987]. Protrusio can also be detected by computed tomography (CT) or magnetic resonance imaging (MRI), if these studies had already been performed and involved axial images of the hips.

Ocular System

Major criterion.
- ectopia lentis

Minor criteria.
- abnormally flat cornea (as measured by keratometry)
- increased axial length of globe (as measured by ultrasound)
- hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis

For the ocular system to be involved, at least 2 of the minor criteria must be present.

Comments. Adequate evaluation of ectopia lentis requires full pupillary dilatation and slit-lamp examination. Dislocation can be unilateral or bilateral, and in any direction (although superior displacement is the usual finding). Iridodonesis (fluttering of the iris) generally is secondary to ectopia lentis; hence, it is not counted as a separate sign of the Marfan syndrome. The radius of curvature of the cornea should be studied by keratometry. The degree of flattening is positively correlated with the presence of ectopia lentis [Mash et al., 1975; Maumenee, 1981]. Megalocornea occurs only occasionally in Marfan syndrome, and is not counted as a minor manifestation. The axial length of the globe in Marfan syndrome usually is increased (normal axial length in an adult is < 23.5 mm) [Fledelius, 1981]. The exaggerated axial length produces myopia and is a major contributor to retinal detachment; hence, the latter findings are not counted as separate manifestations. Hypoplasia of the ciliary muscle is found only in connection with hypoplasia of the iris. Therefore, the presence of either or both anomalies is counted as only one minor criterion. Some experts consider early development of nuclear cataracts and open angle glaucoma typical of Marfan syndrome; these signs need further evaluation before inclusion among the minor criteria.

Cardiovascular System

Major criteria.
- dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva; or
- dissection of the ascending aorta

Minor criteria.
- mitral valve prolapse with or without mitral valve regurgitation;
- dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, below the age of 40 years;

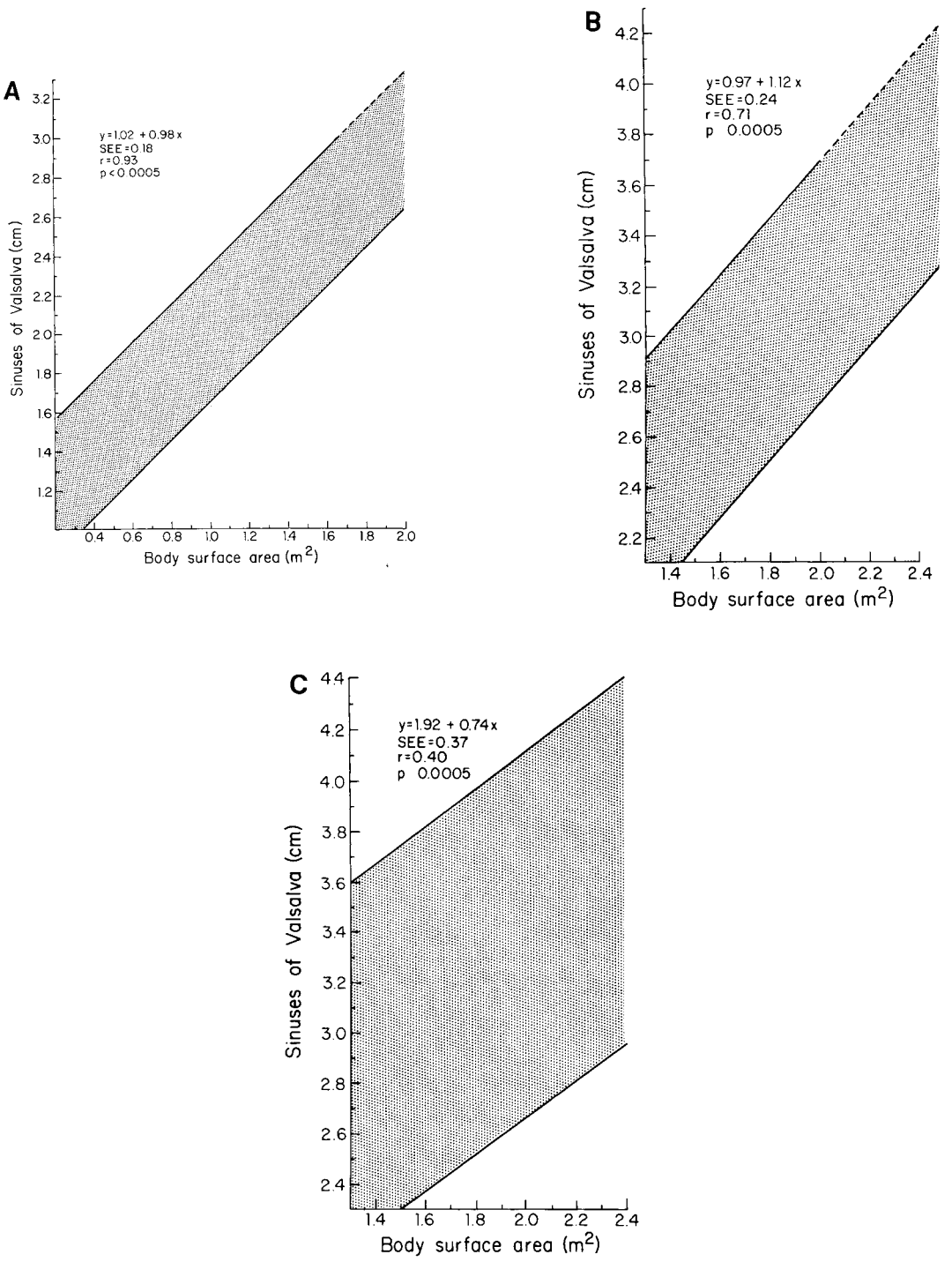

Figure 1. The normal range of aortic root dimensions. 95% confidence interval for sinus of Valsalva diameter versus body surface area for: A. Infants and children; B. Adults < 40 years old; C. Adults ≥ 40 years old. The diameters were measured from cross-sectional echocardiographic images in the parasternal long-axis orientation. Reproduced with permission from Roman et al; (1889a): Two dimensional aortic root dimensions in normal children and adults. Am. J Cardiol 64: 507-512.

- calcification of the mitral annulus below the age of 40 years; or
- dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years

For the cardiovascular system to be involved a major criterion or only one of the minor criteria must be present.

Comments. Dilatation of the aortic root is diagnosed when the maximum diameter at the sinuses of Valsalva measured by echocardiography, CT or MRI exceeds the upper normal limits for age and body size (Fig. 1) [Roman et al., 1989a; 1993]. Aortic dissection should be documented by contrast angiography transesophageal echocardiography, CT or MRI. Stringent criteria for diagnosis of mitral valve prolapse should be used, including late systolic prolapse over 2 mm on M-mode echocardiography or leaflet billowing into left atrium in the long-axis view on cross-sectional echocardiography [Devereux et al., 1987]. Until normal values for pulmonary artery diameter are available, dilatation can be detected provisionally by echocardiography, CT or MRI using nomograms for the aorta.

Pulmonary System

Major criteria.
- none

Minor criteria.
- spontaneous pneumothorax [Hall et al., 1984], or
- apical blebs (ascertained by chest radiography)

For the pulmonary system to be involved one of the minor criteria must be present.

Skin and Integument

Major criterion.
- none

Minor criteria.
- striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress, or
- recurrent or incisional herniae

For the skin and integument to be involved one of the minor criteria must be present.

Comments. Striae in Marfan syndrome are localized preferentially on the shoulders, the lower or midback, and the thighs, but are also seen in MASS phenotype [Glesby and Pyeritz, 1989] and whenever the skin of normal people is repetitively or markedly stretched (e.g., pregnancy).

Dura

Major criterion
- lumbosacral dural ectasia by CT or MRI

Minor criteria
- None

For the dura to be involved the major criterion must be present.

Comments. Adequate evaluation for dural ectasia requires CT or MRI of the lumbosacral region (at least showing L5-S1) [Pyeritz et al., 1988]. Dural ectasia is defined by: enlargement of the neural canal anywhere along the spinal column, but nearly always in the lower lumbar and sacral regions; thinning of the cortex of the pedicles and laminae of the vertebrae and widening of the neural foraminae; or an anterior meningocele. Studies evaluating plain radiography of the lumbosacral vertebral column for detection of dural ectasia are in progress [R.C.M.H., personal communication]. Because the true prevalence of dural ectasia in Marfan syndrome is uncertain (but probably greater than 40%), its selection as a major criterion is based on the rarity with which it is seen in other conditions [Stern, 1988]. If the prolonged influence of gravity on cerebrospinal fluid is essential for the progressive dilatation of the dura and consequent erosion of vertebral bone, dural ectasia should be less common in children.

Family/Genetic History

Major criteria.
- having a parent, child or sib who meets these diagnostic criteria independently;
- presence of a mutation in *FBN1* known to cause the Marfan syndrome; or
- presence of a haplotype around *FBN1*, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family

Minor criteria.
- None

For the family/genetic history to be contributory, one of the major criteria must be present.

Comments. When haplotype segregation is employed, the unequivocally diagnosed relative usually is a first-degree relative, but can be a second-degree or more distant relative. Inability to detect a mutation in *FBN1* or a molecular abnormality in fibrillin-1 does not exclude the diagnosis of the Marfan syndrome in a person who meets the clinical criteria.

Requirements of the Diagnosis of the Marfan Syndrome

For the index case:

- If the family/genetic history is not contributory, major criteria in at least 2 different organ systems and involvement of a third organ system
- If a mutation known to cause Marfan syndrome in others is detected, one major criterion in an organ system and involvement of a second organ system

For a relative of an index case:

- presence of a major criterion in the family history and one major criterion in an organ system and involvement of a second organ system

Comments. Nosologic subgrouping within the Marfan phenotype is inappropriate based on present knowledge. In every instance, homocystinuria should be excluded by plasma amino acid analysis in the absence of pyridoxine supplementation.

Conditions To Be Differentiated from the Marfan Syndrome

Marfan syndrome is entry 154700 in the McKusick [1996] tabulation. The following disorders overlap, to varying extents, with Marfan syndrome, but constitute separate entities.

- congenital contractural arachnodactyly (121050) [Viljoen, 1994]
- familial thoracic aortic aneurysm (132900) [Savunen, 1987; Emanuel et al., 1977]; in the past, this condition was called Erdheim cystic medial necrosis.
- familial aortic dissection (132900) [Nicod et al., 1989]
- familial ectopia lentis (129600) [Tsipouras et al., 1992]
- familial Marfan-like habitus (perhaps 154705) [Milewicz et al., 1995]

Requirements for diagnosis: At least the major criterion of the underlying organ system must be present in at least 2 related individuals. Multisystem involvement is not required for diagnosis in these conditions, but may occur. Although McKusick [1996] lumps aortic dissection and aortic aneurysm, experience suggests that some families have a predisposition to dissection of the ascending aorta without prior dilatation of marked degree.

- MASS phenotype (myopia, mitral valve prolapse, mild aortic dilatation (but less than 2 standard deviations above the expected diameter), skin (striae) and skeletal (minor criteria for Marfan syndrome) involvement (157700) [Glesby and Pyeritz, 1989].

Requirements for diagnosis: At least 2 and preferably 3 organ systems should be involved.

- familial mitral valve prolapse syndrome [Devereux et al., 1982; 1986; 1987; Roman et al, 1989b]

Requirements for diagnosis: Mitral valve prolapse segregating as an autosomal dominant trait; mild skeletal manifestations may be present, but there is insufficient evidence of systemic involvement to meet the criteria for MASS phenotype. (McKusick [1996] does not differentiate this from MASS.)

- Stickler syndrome (hereditary arthroophthalmopathy (108300) [Stickler et al., 1965])

Requirements for diagnosis: This is a multi-system disorder, and at least the eye, the craniofacies and one other system should be affected to establish the diagnosis. Typical findings include: high myopia; vitreoretinal degeneration; retinal detachment; deafness; arthropathy; mild (but occasionally marked early in life) spondyloepiphyseal dysplasia; joint hypermobility; midfacial hypoplasia; micrognathia; U-shaped cleft palate; mitral valve prolapse. Includes the Weissenbacher-Zweymüller syndrome.

- Shprintzen-Goldberg syndrome (182212) [Shprintzen and Goldberg, 1982].

Requirements for diagnosis: In addition to skeletal changes suggestive of the Marfan syndrome, patients have craniosynostosis and neurodevelopmental abnormalities. Aortic dilatation may occur.

DISCUSSION

The diagnosis of Marfan syndrome evolved during the first half of this century as new organ systems were found to be involved, that is, as pleiotropy was defined. The first diagnostic criteria to be viewed widely as such were those of McKusick [1956]. Minor revisions occurred [Pyeritz and McKusick, 1979], but the Berlin Nosology was the first concerted effort to address this issue [Beighton et al., 1988].

A number of reasons support the need for uniform, diagnostic criteria for the Marfan syndrome and for revision of the Berlin Nosology. First, Marfan syndrome, while not common, is not rare; current estimates place the prevalence at 1/3-5,000 [Pyeritz, 1996]. Other related connective tissue disorders are likely as common (familial aortic aneurysm) or much more common (MASS phenotype, familial mitral valve prolapse). When coupled with the phenotypic continuum that exists among these disorders, diagnostic dilemmas are a common occurrence in any medical genetics clinic, and occur regularly in the practice of other specialties, such as cardiology,

ophthalmology and orthopaedics.

Second, the clinical implications of these related conditions are different. The natural history may be more protracted, organ system involvement may be less extensive, and morbid consequences may be unlikely. The importance of being able to decide what Marfan syndrome is, and is not, is self-evident for the physician and the patient. Similarly, for the prospective parent who has some findings of Marfan syndrome, or for the new parent or grandparent of a child who has these anomalies, indecision on the part of the physician or genetic counselor, or divergent opinions from multiple consultants, only aggravates a difficult situation.

Third, being labeled as having Marfan syndrome has social, occupational, psychologic and economic consequences. While these may vary among countries, the implications are nearly always negative and heighten the need to avoid false-positive diagnoses.

Fourth, being told that Marfan syndrome is not the correct diagnosis also has implications in terms of recurrent medical follow-up, prophylactic medication and lifestyle. Because failure to take precautions can have deleterious consequences, avoidance of false -negative diagnoses is equally important.

Fifth, the Berlin Nosology was generated before any clear notion of the cause of Marfan syndrome was available. Molecular studies in families with marked intrafamilial variability in clinical severity (ranging from the classic Marfan syndrome presentation to the involvement of multiple organ systems with minor manifestations such as pectus excavatum and mitral valve prolapse), have documented examples of overdiagnosis of Marfan syndrome in the less severely affected individuals [Pereira et al., 1994].

Sixth, considerable clinical research, especially focused on conventional and, eventually, gene therapy, remains to be done. It is essential that subjects within a study be as homogeneous as possible, and that different studies be comparable as to subjects.

Finally, reliable criteria for phenotypic assessment are essential for interpretation of molecular data, resolving controversies about locus heterogeneity in Marfan syndrome [Collod et al., 1994; Dietz et al., 1995], delineation of phenotypes associated with *FBN1* mutations in people who do not satisfy the diagnostic criteria for Marfan syndrome [Kainulainen et al., 1994; Francke et al., 1995], and for delineation of phenotypes that may be due to mutations in other microfibrillar proteins.

One of the weaknesses of the Berlin Nosology is the promulgation of relatively non-specific criteria for diagnosis of a relative upon unequivocal diagnosis of a first-degree relative. In this setting, the only requirement for diagnosis was the identification of a trait that is commonly seen in Marfan syndrome in any two organ systems. This created problems of over-diagnosis or misdiagnosis. The present proposal is more stringent in that, in addition to a family history of Marfan syndrome (which still means identification of an individual in the family who **independently** satisfies diagnostic criteria on clinical grounds alone), the presence of a major clinical manifestation and involvement of a second system are required for definitive diagnosis.

The present proposal also puts greater diagnostic weight on the skeletal involvement, which can now be been used as a major criterion if at least 4 of 8 typical skeletal manifestations are found. This is important especially for establishing the diagnosis in patients lacking major criteria in other organ systems or having only one other cardinal manifestation (e.g., aortic enlargement or ectopia lentis or dural ectasia).

The potential contribution of molecular analysis towards the diagnosis of Marfan syndrome is neither ignored nor over-emphasized with these new criteria. If an individual has inherited by descent either a mutation or a haplotype that has clearly been associated with Marfan syndrome in relatives independently diagnosed on clinical grounds alone, we propose that a major criterion for diagnosis is fulfilled. Another major clinical criterion and involvement of a second system are still required for definitive diagnosis. However, we emphasize that clinical diagnosis of a first-degree relative and co-inheritance of a mutant allele do not constitute separate major criteria for diagnosis. Therefore, molecular data will find greatest diagnostic significance in situations where clinical information concerning a relevant first-degree relative is unavailable, while both clinical and genotype data are available on a second-degree or more distant relative(s). On the other hand, since methods for the characterization of mutations in *FBN1* are not entirely sensitive and the possibility of locus heterogeneity cannot be discarded, the inability to define a *FBN1* mutation or the stringent documentaion of recombination between *FBN1* and the Marfan phenotype do not constitute exclusion criteria.

Although the present proposal aims to select for typical Marfan manifestations to be ascertained as objectively as possible, there remain several potential traps: most manifestations are age-dependent and some are difficult to quantify. Few studies address the sensitivity or specificity of any of the Marfan anomalies. For example, the association between dural ectasia and the Marfan syndrome has only recently

been pointed out [Pyeritz et al., 1988]. Little is known about the exact prevalence of this manifestation in the Marfan syndrome and further studies are warranted to evaluate its validity and specificity as a major criterion for the Marfan syndrome. A further aim of this publication is to provide initial diagnostic criteria for other heritable conditions with partially overlapping phenotypes as an aid to their clinical identification and research evaluation.

In conclusion, we hope that these revised criteria can serve as an international standard for clinical diagnosis of the Marfan syndrome, for comparing results of clinical and molecular studies, and for investigations of genetic heterogeneity and genotype-phenotype correlations. A further aim of this publication is to provide initial diagnostic criteria for heritable conditions whose phenotypes partially overlap those of the Marfan syndrome as an aid to their clinical identification and research evaluation.

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